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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,033	05/11/2001	Pierre Chambon	065691-0222	5081
22428	7590	06/16/2004	EXAMINER	
FOLEY AND LARDNER SUITE 500 3000 K STREET NW WASHINGTON, DC 20007			QIAN, CELINE X	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/853,033

Applicant(s)

CHAMBON ET AL.

Examiner

Celine X Qian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-19 and 21-61 is/are pending in the application.
- 4a) Of the above claim(s) 9,13,15-18,21,22,24-32,35-49,51 and 53-61 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-8,10-12,14,19,23,33,50 and 52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12/1/03
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

Claims 1, 4-19, 21-33 and 35-61 are pending in the application. Claims 9, 13, 15-18, 21, 22, 24-32, 35-49, 51, 53-61 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1, 4-8, 10-12, 14, 19, 23, 33, 50 and 52 are currently under examination.

This Office Action is in response to the Amendment filed on 3/31/04.

Response to Amendment

The objection to claims 33 and 52 has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 1, 2, 4-8, 10-12, 14, 19, 23, 33, 63 and 64 under 35 U.S.C. 112 1st paragraph (written description) has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claim 50 under 35 U.S.C. 112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 1, 4, 5, 7, 8, 10, 11, 19 and 33 under 35 U.S.C. 102 (b) has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 1, 4-8, 10-12, 14, 19, 23, 33 and 52 under 35 U.S.C. 112 1st paragraph is maintained for reasons set forth of the record mailed on 12/31/03 and further discussed below.

Claims 1, 4-8, 10, 11, 12, 14, 19, 23, 33 and 52 are rejected under 35 U.S.C. 103 (a) for reasons discussed below.

Claims 33, 50 and 52 are rejected under 35 U.S.C. 112 2nd paragraph for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-8, 10-12, 14, 19, 23, 33, 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a first transgene comprising Cre recombinase fused to a mutated ER, wherein such mutation result in conditional activation of Cre upon synthetic ligand treatment but not with natural ligand; a second transgene comprising insertion Cre recognition sites loxP flanking the gene of interest, wherein deletion of the gene exhibits a specific transgene dependent phenotype, for example, altered metabolism in adipocytes when both copies of RXR α alleles are disrupted, does not reasonably provide enablement for any transgenic mouse comprising a cell comprising claimed transgenes. Further, the specification does not enable any transgenic mouse without any phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In response to this rejection, Applicants amended claims to recite “a Cre recombinase” and “wherein the recombinase targets and specifically inactivates said DNA sequence of interest in the presence of synthetic ligand.” Applicants assert that these amendments obviate this rejection.

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The argument has been fully considered but deemed unpersuasive. As discussed in the previous office action, the phenotype of the transgenic mouse is a critical element for the enablement of the claimed invention because one of skilled in the art would not know how to use a mouse with the claimed genotype but has no phenotype. The state of art teaches that the phenotype of a transgenic mouse cannot be predicted by its genotype alone. The amendment that recites "wherein the recombinase targets and specifically inactivates said DNA sequence of interest in the presence of synthetic ligand" does not constitute a phenotype because one skilled in the art cannot predict a specific phenotype of the transgenic mouse, which depends on which "DNA of interest" is inactivated and level of inactivation. Therefore, the claimed invention is not enabled to its full scope.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33, 50 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 recites the limitation "said organism" in 8. There is insufficient antecedent basis for this limitation in the claim. The claim does not recite an organism. In addition, the terms "embryonic stem cell", "embryo of said organism" and "adult organism" also renders the claims indefinite because it is unclear embryonic stem cell, embryo from which species or what

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organism Applicants are referring to. It is unclear how a transgenic mouse can be obtained from another organism. The word “derived” also renders the claim indefinite because the nature and derivative process is unknown.

Claim 33 is also rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to develop an embryo to a fertile adult organism.

Regarding claim 50 and 52, the term “a RXR α ” renders the claims indefinite because it is unclear whether it is referring to an endogenous RXR α gene, an heterologous RXR α introduced into the genome, one copy of the RXR α allele, or both copies of the RXR α alleles. The specification discloses the recited phenotype of “altered metabolism...” is for disruption of both copies of the RXR α gene only. As such, the metes and bounds of the claim cannot be established.

Regarding claim 52, the recitation of “at the level of the DNA sequence of interest...” renders the claim indefinite because it is unclear what level Applicants are referring to. In addition, the recitation of “flanked by two recombinase protein recognition sites oriented as a direct repeat” renders the claim indefinite because it is unclear whether the two sites are separated by the DNA of interest or they are “direct repeat.” As such, the metes and bounds of the claim cannot be established.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 4, 5, 7, 8, 10, 11, 19 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feil et al.

Feil et al. teaches that a conditional gene targeting method based on the inducible activity of an engineered DNA recombinase can be advantageous since it can overcome problems such as intra-utero lethality normally which exists in the field of gene knockout in mice (see page 10887, 1st col., 1st paragraph). Feil et al. teaches such conditional targeting method by generating a double transgenic mouse comprising a reporter cassette that comprises tkneo selection marker flanked by two lox P sites that integrated into RXR α allele, and another cassette comprising Cre-ER^T under the control of CMV promoter (see page 10888, 2nd col., 2-4 paragraph). Feil et al. further disclose OHT administration resulted Cre-mediated excision of tkneo gene (see page 10888, 2nd col., 4th paragraph). However, Feil et al. do not teach that the excised DNA sequence is an endogenous gene.

It would have been obvious to one of ordinary skill of art to modified the conditional targeting method taught by Feil et al. to have an endogenous gene, such as RXR α or intergenic sequence flanked by loxP sites (instead of a test gene) based on the teaching of Feil et al. One of ordinary skill in the art would have been motivated to do so because the purpose of the method taught by Feil et al. is to conditionally inactivate endogenous gene within mouse genome (see page 10887, 1st col., 1st paragraph). The level of skill in the art is high, inserting lox P sites next to an endogenous gene such as RXR α or to a test gene is routine experimentation. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of

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success to make modification such as inserting loxP site at a different place. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Feil et al., in view of Schwenk et al.

The teaching of Feil et al. is discussed above. However, Feil et al. do not teach a transgenic mouse comprising a transgene comprising a D hinge region of SEQ ID NO:2 from 282-301.

Schwenk et al. teach the generation of a fusion construct comprising Cre and a VRGS linker and ligand binding domain of ER starting from amino acid 304 (see page 1427, 2nd col., 4th paragraph). Schwenk et al. teach that such construct is ligand inducible and capable of generate B cell specific gene deletion in mice (see page 1430, 3rd paragraph).

The obviousness of making a transgenic mouse comprising Cre-ER^T under the control of CMV promoter, and loxP2 sites inserted next to gene or intergenic DNA of interest is discussed above.

It would have been obvious to one of ordinary skill of art to use any linker for attachment of ER ligand binding domain to Cre recombinase based on the teaching of Feil et al. and Schwenk et al. because the linker does not affect the conditional induction of Cre recombinase. One of ordinary skill in the art would have been motivated to use D hinge region of SEQ ID NO:2 from 282-301 as linker to fuse to the Cre and human ER because it is native to the human ER and ease of manipulation. The level of skill in the art of molecular cloning is high. Absent evidence to the contrary, one of ordinary skill of art would have reasonable expectation of

success to fuse human ER with D hinge region from 282-301 with Cre recombinase. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Claims 12, 14, 23 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feil et al., in view of Indra et al., Ross et al. and Tontonoz et al. (1997, PNAS, Vol.94, pp.237-241)

The teachings of Feil et al. are discussed above. However, Feil et al. do not teaches a transgenic mouse comprising RXR α flanked by two lox P sites, and another cassette comprising Cre-ER^T under the control of aP2 promoter.

Indra et al. disclose that transgenic mice comprising Cre-ER^{T2} under the control of K5 promoter are crossed with reporter mice which comprises loxP-CAT-loxP-lacZ cassette, and subsequently mice with both transgene cassette are generated (see page 4326, col.1). Indra et al. further disclose that oral or topical tamoxifen administration results selective deletion of the CAT gene and results in β -gal staining in mouse keratinocytes (see page 4326, col.1).

Ross et al. teach an adipocyte specific promoter aP2 that confer adipocyte specific expression in transgenic mouse (see abstract and Table 1). Ross et al. further teach a 5.4 kb 5' flanking region of aP2 gene confers the highest promoter activity (see Figure 1B).

Tontonoz et al. teach peroxisome proliferator-activated receptor and RXR α form a heterodimeric complex that functions as a central regulator of adipocyte differentiation (see page 237, 2nd col., 2nd paragraph). Tontonoz et al. also teach that activators of RXR α may be useful in treating liposarcoma in humans because the regulatory role of RXR α plays in adipocyte differentiation.

The obviousness of making a transgenic mouse comprising Cre-ER^T under the control of CMV promoter, and loxP2 sites inserted next to gene or intergenic DNA of interest is discussed above.

It would have been obvious to one of ordinary skill of art to make a transgenic mouse with selective RXR α disruption in adipose tissue based on the combined teaching of Indra et al. and Feil et al., Ross et al. and Tontonoz et al. The ordinary skilled artisan would have been motivated to do so to study the precise function of RXR α because the implication of RXR α 's role in regulating adipocyte differentiation and possible role as a target for pharmacological intervention of liposarcoma in humans. Based on the teaching of Indra et al and Feil et al., one of ordinary skill of art would make a such a transgenic mouse by crossing the transgenic mouse comprising a Cre-ER fusion protein under control of aP2 promoter (as taught by Ross et al.) and a second transgenic mouse comprising modified RXR α allele comprising lox P sites to generate a double transgenic mouse, and subsequently treating the offspring with tamoxifen to induce tissue specific Cre expression and result in excision of the RXR α target gene. The level of skill in the art is high. Absent evidence to the contrary, one ordinary skill of art would have reasonable expectation of success to make such double transgenic mouse. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

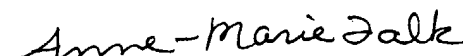
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.


ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER